

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



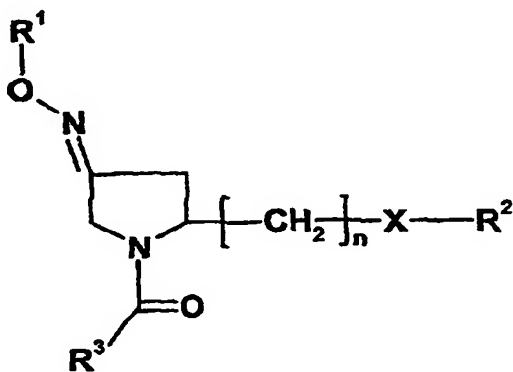
(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/005249 A1

- (51) International Patent Classification⁷: C07D 207/22, 521/00, 403/06, A61K 31/4025, A61P 5/10
- (74) Agent: SERONO INTERNATIONAL S.A.; Intellectual Property, 12, chemin des Aulx, CH-1228 Plan-les-Ouates (CH).
- (21) International Application Number: PCT/EP2003/050286
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 4 July 2003 (04.07.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 02100784.4 5 July 2002 (05.07.2002) EP
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. [NL/NL]; Pietermaai 15, NL- Curaçao (AN).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): JORAND-LEBRUN, Catherine [FR/FR]; Chef Lieu, F-74270 Contamine-Sarzin (FR). DORBAIS, Jérôme [FR/FR]; 5, rue Burgat-Charvillon, F-74000 Annecy (FR). QUATROPANI, Anna [CH/CH]; Rue de la Filature 20, CH-1227 Carouge (CH). SCHWARZ, Matthias [CH/CH]; Av. Tronchet 32 B, CH-1226 Thonex (CH). VALOGNES, Delphine [FR/FR]; Murcier, F-74520 Savigny (FR).
- Published:
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRROLIDINE DERIVATIVES AS OXYTOCIN ANTAGONISTS



(I)

(57) Abstract: The present invention relates to novel pyrrolidine derivative of formula (I), its geometrical isomers, its optically active forms as enantiomers, diastereomers, mixtures of these and its racemate forms, as well as salts thereof, wherein R¹ is selected from the group comprising or consisting of H and C₁-C₆-alkyl, for the prevention and/or treatment of preterm labor, premature birth or dysmenorrhea.

WO 2004/005249 A1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50286

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/22 C07D521/00 C07D403/06 A61K31/4025 A61P5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 72705 A (QUATTROPANI ANNA ;SCHEER ALEXANDER (CH); SCHWARZ MATTHIAS (CH); HA) 4 October 2001 (2001-10-04) cited in the application page 178 -page 179; table 1 page 181; table 2 page 183; table 3 page 185; table 4	1,8
A	WO 99 52868 A (ALMSTEAD NEIL GREGORY ;TAIWO YETUNDE OLABISI (US); BISWANATH DE (U) 21 October 1999 (1999-10-21) page 18, paragraph 5 example 3	1,8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

3 November 2003

Date of mailing of the international search report

20/11/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50286

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50286

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0172705	A	04-10-2001	AU 5620901 A	08-10-2001
			BG 107132 A	30-04-2003
			BR 0109900 A	03-06-2003
			CA 2401242 A1	04-10-2001
			CN 1419541 T	21-05-2003
			CZ 20023243 A3	15-01-2003
			WO 0172705 A1	04-10-2001
			EP 1268419 A1	02-01-2003
			HU 0300994 A2	28-08-2003
			JP 2003528854 T	30-09-2003
			NO 20024598 A	25-11-2002
			SK 13832002 A3	04-03-2003
WO 9952868	A	21-10-1999	AU 753048 B2	03-10-2002
			AU 3552299 A	01-11-1999
			BR 9909620 A	19-12-2000
			CA 2328211 A1	21-10-1999
			CN 1297436 T	30-05-2001
			EP 1073635 A1	07-02-2001
			HU 0102195 A2	28-11-2001
			JP 2002511448 T	16-04-2002
			NO 20005196 A	14-12-2000
			NZ 507076 A	29-04-2003
			PL 343529 A1	27-08-2001
			SK 15462000 A3	11-06-2001
			TR 200002971 T2	21-02-2001
			WO 9952868 A1	21-10-1999
			US 6329418 B1	11-12-2001
			ZA 200005047 A	06-06-2001

PATENT COOPERATION TREATY

Serono International S.A.

01. März 2004

PCT

Corporate IP Dept.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SERONO INTERNATIONAL S.A.
Intellectual Property
12, Chemin des Aulx
CH-1228 Plan-Les-Ouates
SUISSE

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

01/03/2004

Applicant's or agent's file reference

WO 479

IMPORTANT NOTIFICATION

International application No.

PCT/EP03/50286

International filing date (day/month/year)

04/07/2003

Priority date (day/month/year)

05/07/2002

Applicant

APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/

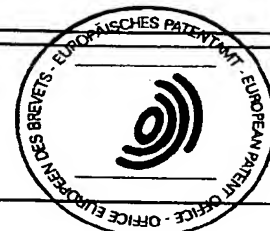


European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

ROSSI C

Tel. (+49-89) 2399 2828



PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)


Applicant's or agent's file reference WO 479	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP03/50286	International filing date (<i>day/month/year</i>) 04/07/2003	Priority date (<i>day/month/year</i>) 05/07/2002
International Patent Classification (IPC) or national classification and IPC C07D207/22		
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.		

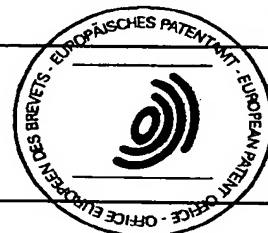
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 2 sheets, including this cover sheet.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 02/02/2004	Date of completion of this report 25/02/2004
Name and mailing address of the IPEA/  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer VERHULST W Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No.

PCT/EP03/50286

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)


Applicant's or agent's file reference WO 479	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
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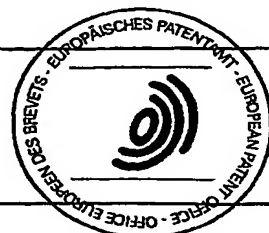
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/03/50286

A. CLASSIFICATION OF SUBJECT MATTER:

IPC 7 C07D207/22 C07D521/00 C07D403/06 A61K31/4025 A61P5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of box C.

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- *G* document member of the same patent family

Date of the actual completion of the international search

3 November 2003

Date of mailing of the international search report

20/11/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

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Seitner, I

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/03/50286

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0172705	A	04-10-2001	AU 5620901 A	08-10-2001
			BG 107132 A	30-04-2003
			BR 0109900 A	03-06-2003
			CA 2401242 A1	04-10-2001
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			CZ 20023243 A3	15-01-2003
			WO 0172705 A1	04-10-2001
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			NO 20024598 A	25-11-2002
			SK 13832002 A3	04-03-2003
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WO 9952868	A	21-10-1999	AU 753048 B2	03-10-2002
			AU 3552299 A	01-11-1999
			BR 9909620 A	19-12-2000
			CA 2328211 A1	21-10-1999
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			HU 0102195 A2	28-11-2001
			JP 2002511448 T	16-04-2002
			NO 20005196 A	14-12-2000
			NZ 507076 A	29-04-2003
			PL 343529 A1	27-08-2001
			SK 15462000 A3	11-06-2001
			TR 200002971 T2	21-02-2001
			WO 9952868 A1	21-10-1999
			US 6329418 B1	11-12-2001
			ZA 200005047 A	06-06-2001